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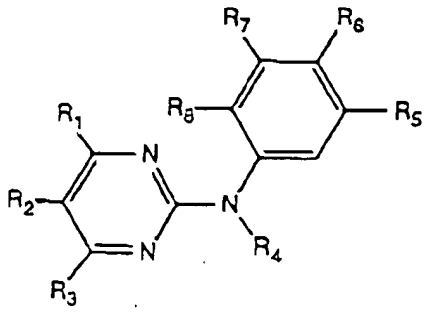
(54) **Use of pyrimidine derivatives as protein kinase C-inhibitors and anti-tumor agents.**

(57) The invention relates to the use of known N-phenyl-2-pyrimidinamine derivatives of formula I for the inhibition of protein kinase C in warm-blooded animals, i.e. for example as anti-tumor agents.



(I)

The substituents in formula I have the meanings given in Claim 1.

EP 0 588 762 A1

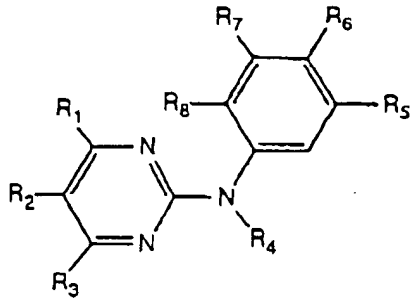
The invention relates to the use of known N-phenyl-2-pyrimidinamine derivatives for the inhibition of protein kinase C and/or as anti-tumor agents as well as for the production of pharmaceutical preparations for use as inhibitors of protein kinase C and/or as anti-tumor agents in warm-blooded animals.

The European patent application with the application number 87100277.0, which was published on 8/26/1987 under the publication number 0233461, and which is in part equivalent to US patent No. 4,876,252, describes N-phenyl-2-pyrimidinamine derivatives, their preparation and their use as anti-asthmatic and anti-allergic agents on the basis of the inhibition of histamine release, as well as their use in inflammation and diabetes.

According to the invention, it has now been found that some of the N-phenyl-2-pyrimidinamine derivatives described in EP-A-0233461 selectively inhibit the enzyme protein kinase C.

Protein kinase C, dependant on phospholipids and calcium, is present inside the cells in several species (distribution of the species tissue-specific) and participate in various fundamental processes, such as signal transmission, proliferation and differentiation, as well as release of hormones and neurotransmitters. The activation of this enzyme results either by means of a hydrolysis of phospholipids of the cell membrane mediated by receptors or by means of a direct interaction with certain tumor-promoting active substances. Cellular functions that are controlled by protein kinase C can be influenced by the modulation of the enzyme activity of protein kinase C.

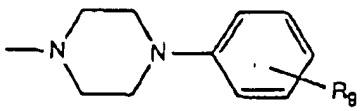
The invention relates to the use of N-phenyl-2-pyrimidinamine derivatives of formula I,



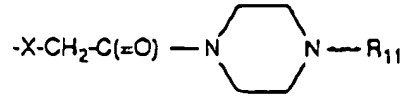
(I)

in which R_1 is hydrogen or C_1-C_3-alkyl, R_2 is hydrogen or C_1-C_3-alkyl, R_3 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-yl-iodide, dimethylamino-phenyl or N-acetyl-N-methyl-aminophenyl, R_4 is hydrogen, C_1-C_3-alkyl-alkyl, the residue -CO-CO-OC_2H_5 or N,N-dimethylaminoethyl, at least one of the residues R_5, R_6, R_7 and R_8 is C_1-C_6-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono-(C_1-C_3-alkyl)-amino, di-(C_1-C_3-alkyl)-amino, C_2-C_4-alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di-(C_1-C_3-alkyl)-sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl, or a residue of one of the formulas:

-CO_2R, -NH-C(=O)-R, -N(R)-C(=O)-R, -O-$(CH_2)_n$-N(R)-R, -C(=O)-NH-$(CH_2)_n$-N(R)R, -$CH(CH_3)$-NH-CHO, -$C(CH_3)$=N-OH, -$C(CH_3)$=N-O-CH_3,
-$C(CH_3)$-NH_2, -NH-CH_2-C(=O)-N(R)R,



-$(CH_2)_m$-R_{10}, -X-$(CH_2)_m$-R_{10} or



in which R stands for C_1-C_3-alkyl, X for oxygen or sulfur, m for 1, 2 or 3, n for 2 or 3, R_9 for hydrogen, C_1-C_3-

alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine or trifluoromethyl, R_{10} for 1H-imidazol-1-yl or morpholinyl, and R_{11} for C_1-C_3-alkyl or unsubstituted phenyl or phenyl mono-substituted by C_1-C_3-alkyl, halogen or trifluoromethyl, and the rest of the residues R_5, R_6, R_7 and R_8 are hydrogen, or of pharmaceutically useful salts of such compounds with at least one salt-forming group for the inhibition of protein kinase C and for the production of pharmaceutical preparations for use as inhibitors of protein kinase C in warm-blooded animals. The use in accordance with the invention as inhibitors of protein kinase C does not extend to the previously described applications against asthma, allergies, inflammation and diabetes, even if the action against these diseases was causally attributed to the inhibition of protein kinase C.

The compounds of formula I and their preparation are described in EP-A-0233461 and in US patent 4,876,252.

Salt-forming groups in a compound of formula I are groups or residues with basic or acidic properties. Compounds with at least one basic group or at least one basic residue, for example a free amino group or a pyridyl residue can form acid addition salts, e.g. with inorganic acids such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids, e.g. aliphatic mono- or dicarboxylic acids, such as trifluoroacetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid, oxalic acid, or amino acids, such as arginine or lysine, aromatic carboxylic acids such as benzoic acid, 2-phenoxy-benzoic acid, 2-acetoxybenzoic acid, salicylic acid, 4-aminosalicylic acid, aromatic-aliphatic carboxylic acids such as mandelic acid or cinnamic acid, heteroaromatic carboxylic acids such as nicotinic acid or isonicotinic acid, aliphatic sulfonic acids such as methane-, ethane-, or 2-hydroxy-ethane-sulfonic acid, or aromatic sulfonic acids, e.g. benzene-, p-toluene-, or naphthalene-2-sulfonic acid. In the presence of several basic groups, mono- or poly-acid addition salts can be formed.

Compounds of formula I with acidic groups, e.g. a free carboxyl group, can form metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g. sodium, potassium, magnesium, or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary mono-amines, e.g. triethylamine or tri-(2-hydroxyethyl)-amine, or heterocyclic bases, e.g. N-ethyl-piperidine or N,N'-dimethyl-piperazine.

As has been found according to the invention, the compounds of formula I possess hitherto unknown, valuable pharmacological properties, e.g. they selectively inhibit the enzyme protein kinase C.

For the determination of the protein kinase C-inhibitory action, protein kinase C from swine brain is used. The determination of the protein kinase C-inhibitory action of compounds of formula I takes place by the method of D. Fabbro et al. as described in Example 2. In this test, the compounds of formula I already inhibit protein kinase C at an IC_{50} concentration of between 1 and 30 µmol/liter.

In contrast to this, the compounds of formula I inhibit other enzymes, e.g. protein kinase A and protein phosphorylase kinase, only at a much higher concentration, e.g. 100 times higher. This shows the selectivity of the compounds of formula I.

Based on their inhibitory action against protein kinase C, the compounds of formula I and their pharmaceutically useful salts can be used as tumor-inhibiting, immuno-modulatory and antibacterial active substances, and also as agents against atherosclerosis, the immune deficiency disease AIDS, as well as diseases of the cardiovascular system and the central nervous system.

As can already be anticipated on the basis of the above-described inhibitory action on protein kinase C, the compounds of formula I display antiproliferative properties that can, among other things, be directly demonstrated in the experiment described in Example 1. The inhibitory action of the compounds of formula I on the growth of human T24 bladder carcinoma cells is thereby determined. The IC_{50} values thus reported for the compounds of formula I are between 1 and 10 µmol/liter.

The antiproliferative action can also be demonstrated in vivo, e.g. as described in Example 3. In the experiment described in Example 3, the compounds of formula I, after peroral or intraperitoneal administration, cause a reduction in the tumor volume to about 35-70% of the tumor volume in control animals treated with placebo.

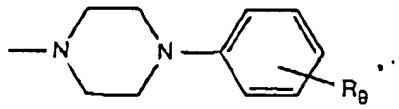
Based on the properties described, the compounds of formula I can be used in particular as tumor-inhibiting active substances, e.g. for the treatment of tumors of the bladder. The invention relates to this use as an anti-tumor agent independently of whether the anti-tumoral action is causally attributable to the inhibition of protein kinase C or not, and independently of whether it can be demonstrated that the anti-tumoral action found is causally attributed to the inhibition of protein kinase C.

If the compounds of formula I are used in cancer treatment in combination with other chemotherapeutic agents, they impede the building of resistance (multidrug resistance) or neutralize an already-existing resistance to other chemotherapeutic agents. In addition to this, the compounds of formula I are suitable for the further applications mentioned above for protein kinase C modulators and can in particular be used for the treatment of diseases that respond to an inhibition of protein kinase C. The invention relates to the use of the compounds of formula I for the above-mentioned purposes, with the exception of the above-described use against asthma, allergies, inflammation and diabetes, and for the preparation of pharmaceutical preparations for use for these purposes.

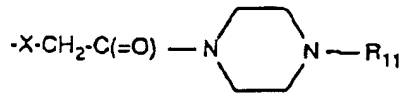
Preferably, compounds of formula I are used in which at least two of the residues R_5, R_6 and R_8 each stand for hydrogen, in particular those compounds in which R_5, R_8 and R_9 each stand for hydrogen and the other substituents in each case have the above-mentioned meanings, and pharmaceutically useful salts of such compounds with at least one salt-forming group.

Compounds of formula I are chiefly used in which R_1, R_2, R_4, R_5, R_6 and R_8 each stand for hydrogen, R_3 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-yl-iodide, dimethylamino-phenyl or N-acetyl-N-methyl-aminophenyl, R_7 is C_1-C_6-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono-(C_1-C_3-alkyl)-amino, di-(C_1-C_3-alkyl)-amino, C_2-C_4-alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di-(C_1-C_3-alkyl)-sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl, or a residue of one of the formulas:

$-CO_2R$, $-NH-C(=O)-R$, $-N(R)-C(=O)-R$, $-O-(CH_2)_n-N(R)-R$, $-C(=O)-NH-(CH_2)_n-N(R)R$, $-CH(CH_3)-NH-CHO$, $-C(CH_3)=N-OH$, $-C(CH_3)=N-O-CH_3$,
$-C(CH_3)-NH_2$, $-NH-CH_2-C(=O)-N(R)R$,



$-(CH_2)_m-R_{10}$, $-X-(CH_2)_m-R_{10}$ or



in which R stands for C_1-C_3-alkyl, X for oxygen or sulfur, m for 1, 2 or 3, n for 2 or 3, R_9 for hydrogen, C_1-C_3-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine or trifluoromethyl, R_{10} for 1H-imidazol-1-yl or morpholinyl, and R_{11} for C_1-C_3-alkyl or unsubstituted phenyl or phenyl mono-substituted by C_1-C_3-alkyl, halogen or trifluoromethyl, and pharmaceutically useful salts of such compounds with at least one salt-forming group.

Particularly preferably used are compounds of formula I in which R_1, R_2, R_4, R_5, R_6 and R_8 each stand for hydrogen, R_3 is 3-pyridyl, and R_7 is 1H-imidazol-1-yl, amino, trifluoromethyl, chlorine or a residue of formula $-CO_2R$ or $C(=O)-NH-(CH_2)_n-N(R)-R$ in which each R is hydrogen or methyl and n is 3, and pharmaceutically useful acid addition salts of such compounds.

Most preferably used of all are the compounds of formula I cited in the examples and pharmaceutically useful acid addition salts of such compounds.

The invention also relates to a method for the treatment of warm-blooded animals that suffer from a tumoral disease, in which warm-blooded animals that need such a treatment are given an efficacious tumor-inhibiting amount of a compound of formula I or a pharmaceutically useful salt thereof. The invention also relates to the use of a compound of formula I or a pharmaceutically useful salt thereof for the inhibition of protein kinase C in warm-blooded animals or for preparation of pharmaceutical preparations for use for the therapeutic treatment of the human or animal body. The invention also relates to a method for inhibiting protein kinase C in warm-blooded animals whereby warm-blooded animals that need such a treatment are given an efficacious protein kinase C-inhibiting amount of a compound of formula I. For this, a warm-blooded animal of body weight ca. 70 kg, depending on species, age, individual condition, mode of application, and the respective clinical picture is given enteral or parenteral daily doses of about 1-2000 mg, in particular 50-2000 mg, mainly 500-2000 mg, e.g. 500-1000 mg.

The invention also relates to the use of a compound of formula I or a pharmaceutically useful salt thereof for the production of pharmaceutical preparations for use for the inhibition of protein kinase C, e.g. for the treatment of tumoral diseases. The pharmaceutical preparations referred to contain an efficacious amount, in particular an amount efficacious for the prophylaxis or treatment of one of the above-mentioned diseases, of the active substance together with pharmaceutically useful carrier substances that are suited to topical, enteral, e.g. oral or rectal, or parenteral administration and can be inorganic or organic, solid or liquid. For oral administration, tablets or gelatine capsules are in particular used that contain the active substance together with diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycerol, and/or lubricants, e.g. silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets can also contain binders, e.g. magnesium aluminum silicate, starches, such as corn, wheat or rice starch, gelatins, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone and, if desired, disintegrants, e.g. starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures, or adsorbents, coloring agents, flavorings and sweeteners. In addition, the pharmacologically active compounds of the present invention can be used in the form of parenterally-administered preparations or infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions, so that these, e.g. with lyophilized preparations that contain the active substance alone or together with a carrier material, e.g. mannitol, can be prepared before use. The pharmaceutical preparations can be sterilized and/or contain inert ingredients, e.g. preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical preparations that, if desired, can contain other pharmaceutically active substances such as antibiotics, are prepared in ways known in the art, e.g. by conventional mixing, granulating, tableting, dissolving or lyophilizing methods, and contain from about 1% to 100%, in particular from about 1% to about 20% of the active substance(s).

The following examples illustrate the invention without in any way limiting it.

Abbreviations:

Compound A = N-(3-1H-imidazol-1-yl-phenyl)-4-(3-pyridyl)-2-pyrimidinamine (= compound of formula I, in which R_1, R_2, R_4, R_5, R_6 and R_8 each stand for hydrogen, R_3 is 3-pyridyl, and R_7 is 1H-imidazol-1-yl)

Compound B = N-(3-trifluoromethyl-phenyl)-4-(3-pyridyl)-2-pyrimidinamine [typo in original]

Compound C = N-(3-chlorophenyl)-4-(3-pyridyl)-2-pyrimidinamine

Compound D = N-(3-aminophenyl)-4-(3-pyridyl)-2-pyrimidinamine

Compound E = N-(3-methoxycarbonyl-phenyl)-4-(3-pyridyl)-2-pyrimidinamine

Compound F = N-(3-[3-amino-propylamino-carbonyl]-phenyl)-4-(3-pyridyl)-2-pyrimidinamine.

Example 1: Inhibition of the growth of human bladder carcinoma cells

Human T24 bladder carcinoma cells are incubated in "Eagle's minimal essential medium" to which has been added 5% (v/v) fetal calf serum, in a moist incubator at 37°C and 5 percent by volume CO_2 in the air. The

carcinoma cells (1000-1500) are inoculated in 96-well microtitration plates and incubated overnight under the above-mentioned conditions. The test substance is added in serial dilutions on day 1. The plates are incubated for 5 days under the above-mentioned conditions. During this period, the control cultures undergo at least 4 cell divisions. After the incubation, the cells are fixed with 3.3% (w/v) aqueous glutaraldehyde solution, washed with water and stained with 0.05% (w/v) aqueous methylene blue solution. After washing, the stain is eluted with 3% (w/v) aqueous hydrochloric acid. Then the optical density (OD) per well, which is directly proportional to the number of cells, is measured with a photometer (Titertek multiskan) at 665 nm. The IC_{50} values are calculated with a computer system using the formula

$$\frac{OD_{665}\text{ (Test) minus }OD_{665}\text{ (Start)}}{OD_{665}\text{ (Control) minus }OD_{665}\text{ (Start)}} \times 100$$

The IC_{50} values are defined as that concentration of active substance at which the number of cells per well at the end of the incubation period is only 50% of the number of cells in the control cultures. In the test described, the following IC_{50} values are obtained for compounds of formula I:

Compound	[µMol/Liter]
A	2.5
B	7.4
C	5.2
D	7.2

Example 2: Determination of the protein kinase C inhibitory action

For the determination of the protein kinase C inhibitory action, protein kinase C from swine brain is used, which is purified according to the method described by T. Uchida and C.R. Filburn in J. Biol. Chem. 259, 12311-4 (1984). The determination of the protein kinase C inhibitory action of the compounds of formula I takes place according to the method of D. Fabbro et al., Arch. Biochem. Biophys. 239, 102-111 (1985). In the test described, the following IC_{50} values were obtained for compounds of formula I:

Compound	[µMol/Liter]
A	8.8
B	2.5
C	6.3
D	28
E	26
F	28

Example 3: Anti-tumoral activity in mice

On Day 0, an approximately 25-mg piece of a human T24 bladder carcinoma is transplanted subcutaneously by means of a trocar under surgical "Forene" anesthesia on to each female Balb/c nude mouse (Balb/c nu/nu, Bomholdgaard, Denmark; six mice per group). On Day 6 after the transplantation of the tumor, the average tumor volume is 120-140 mm^3 and the treatment is begun which consists of administering perorally or

intraperitoneally once a day on 15 consecutive days, i.e. a total of 15 times, 25 ml/kg of the formulation below. This formulation is prepared as follows: 16 mg of an active substance of formula I are dissolved in 0.4 ml dimethylsulfoxide (100%).

To this is added 0.05 ml Tween 80 and mixed. Then 7.6 ml of a 0.9% aqueous sodium chloride solution is added and immediately mixed thoroughly. This formulation is made fresh daily. The control animals receive a placebo. As placebo is used the same formulation without the active substance of formula I.

24 hours after the last application, the tumor volume is measured and the ratio (%) of the tumor volume T/C in the treated animals (T) and control animals (C) treated with placebo is determined, with the tumor volume in the control animals being defined as 100%, that is, the smaller the T/C ratio, the more effective is the formulation administered.

If Compound B is used as the active substance of formula I, then on peroral administration of 25 or 50 mg Compound B in the above experiment, a ratio T/C of 68% or 53% is reported. On intraperitoneal administration of 25 or 50 mg Compound B in the above experiment, a T/C ratio of 54% or 46% is reported.

Example 4:

Tablets containing 20 mg active substance, e.g. one of the compounds of formula I cited in Examples 1 and 2, are prepared in the following composition in the usual way:

Composition	
Active substance	20 mg
Wheat starch	60 mg
Milk sugar	50 mg
Colloidal silica	5 mg
Talc	9 mg
Magnesium stearate	1 mg
	145 mg

Preparation:

The active substance is mixed with part of the wheat starch, with milk sugar and colloidal silica, and the mixture is passed through a sieve. Another part of the wheat starch is made into a paste with a 5-fold quantity of water on the water-bath and the powder mixture is kneaded with this paste until a weakly plastic mass results.

The plastic mass is pressed through a sieve of ca. 3 mm mesh width, dried and the dry granulate obtained is again passed through a sieve. Then the remaining wheat starch, talc and magnesium stearate are mixed in and the mixture is compressed into scored tablets of weight 145 mg.

Example 5:

Tablets containing 1 mg active substance, e.g. one of the compounds of formula I cited in Examples 1-2, are prepared in the following manner:

Composition	
Active substance	1 mg
Wheat starch	60 mg
Milk sugar	50 mg
Colloidal silica	5 mg
Talc	9 mg
Magnesium stearate	1 mg
	126 mg

Preparation:

The active substance is mixed with part of the wheat starch, milk sugar and colloidal silica and the mixture is passed through a sieve. Another part of the wheat starch is made into a paste with a 5-fold quantity of water on the water-bath and the powder mixture is kneaded with this paste until a weakly plastic mass results.

The plastic mass is pressed through a sieve of ca. 3 mm mesh width, dried and the dry granulate obtained is again passed through a sieve. Then the remaining wheat starch, talc and magnesium stearate is mixed in and the mixture is compressed into scored tablets of weight 126 mg.

Example 6:

Capsules containing 10 mg active substance, e.g. one of the compounds of formula I cited in Examples 1-2, are prepared as follows in the usual manner:

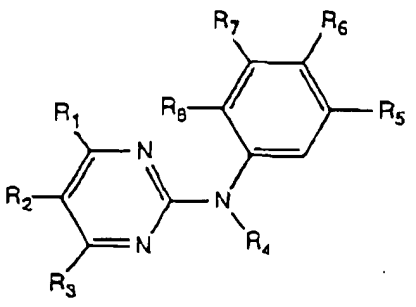
Composition	
Active substance	2500 mg
Talc	200 mg
Colloidal silica	50 mg

Preparation:

The active substance is mixed intimately with talc and colloidal silica, the mixture is passed through a sieve of 0.5 mm mesh width, and hard gelatin capsules of appropriate size are each filled with 11-mg portions of this mixture.

Patent claims

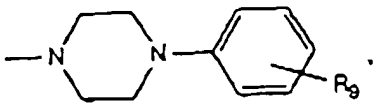
1. Use of N-phenyl-2-pyrimidinamine derivatives of formula I,



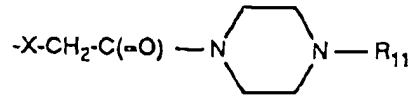
(I)

in which R_1 stands for hydrogen or C_1-C_3-alkyl, R_2 is hydrogen or C_1-C_3-alkyl, R_3 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-yl-iodide, dimethylamino-phenyl or N-acetyl-N-methyl-aminophenyl, R_4 is hydrogen, C_1-C_3-alkyl-alkyl, the residue -CO-CO-OC_2H_5 or N,N-dimethylaminoethyl, at least one of the residues R_5, R_6, R_7 and R_8 is C_1-C_6-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono-(C_1-C_3-alkyl)-amino, di-(C_1-C_3-alkyl)-amino, C_2-C_4-alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di-(C_1-C_3-alkyl)-sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl, or a residue of one of the formulas:

$-CO_2R$, -NH-C(=O)-R, -N(R)-C(=O)-R, -O-$(CH_2)_n$-N(R)-R, -C(=O)-NH-$(CH_2)_n$-N(R)R, $-CH(CH_3)$-NH-CHO, $-C(CH_3)$=N-OH, $-C(CH_3)$=N-O-CH_3,
$-C(CH_3)-NH_2$, -NH-CH_2-C(=O)-N(R)R,



$-(CH_2)_m-R_{10}$, $-X-(CH_2)_m-R_{10}$ or

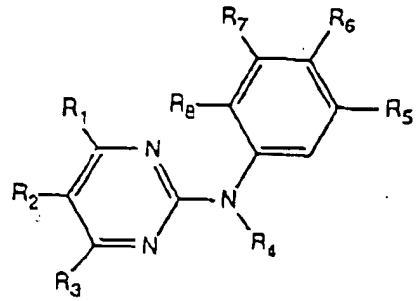


in which R stands for C_1-C_3-alkyl, X for oxygen or sulfur, m for 1, 2 or 3, n for 2 or 3, R_9 for hydrogen, C_1-C_3-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine or trifluoromethyl, R_{10} for 1H-imidazol-1-yl or morpholinyl, and R_{11} for C_1-C_3-alkyl or unsubstituted phenyl or phenyl mono-substituted by C_1-C_3-alkyl, halogen or trifluoromethyl, and the rest of the residues R_5, R_6, R_7 and R_8 are hydrogen, or of pharmaceutically acceptable salts of such compounds with at least one salt-forming group for the inhibition of protein kinase C and for the production of pharmaceutical preparations for use as inhibitors of protein kinase C in warm-blooded animals, including humans.

2. Use as in claim 1 for the preparation of pharmaceutical preparations for use as antitumoral agents in warm-blooded animals including humans.

3. Use as in claim 1 with the exception of a possible use against asthma, allergies, inflammation and diabetes.

4. Use of N-phenyl-2-pyrimidinamine derivatives of formula I,

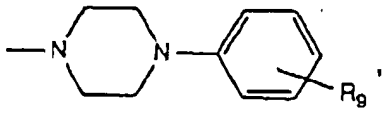


(I)

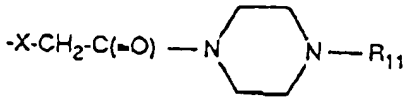
in which R_1 stands for hydrogen or C_1-C_3-alkyl, R_2 is hydrogen or C_1-C_3-alkyl, R_3 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-yl-iodide, dimethylamino-phenyl or N-acetyl-N-methyl-aminophenyl, R_4 is hydrogen, C_1-C_3-alkyl, the residue -CO-CO-OC_2H_5 or N,N-dimethylaminoethyl, at least one of the residues R_5, R_6, R_7 and R_8 is C_1-C_6-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono-(C_1-C_3-alkyl)-amino, di-(C_1-C_3-alkyl)-amino, C_2-C_4-alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-

di-(C_1-C_3-alkyl)-sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or a residue of one of the formulas:

$-CO_2R$, $-NH-C(=O)-R$, $-N(R)-C(=O)-R$, $-O-(CH_2)_n-N(R)-R$, $-C(=O)-NH-(CH_2)_n-N(R)R$, $-CH(CH_3)-NH-CHO$, $-C(CH_3)=N-OH$, $-C(CH_3)=N-O-CH_3$,
$-C(CH_3)-NH_2$, $-NH-CH_2-C(=O)-N(R)R$,



$-(CH_2)_m-R_{10}$, $-X-(CH_2)_m-R_{10}$ or



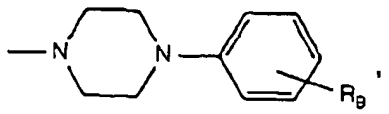
in which R stands for C_1-C_3-alkyl, X for oxygen or sulfur, m for 1, 2 or 3, n for 2 or 3, R_9 for hydrogen, C_1-C_3-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine or trifluoromethyl, R_{10} for 1H-imidazol-1-yl or morpholinyl, and R_{11} for C_1-C_3-alkyl or unsubstituted phenyl or phenyl mono-substituted by C_1-C_3-alkyl, halogen or trifluoromethyl, and the rest of the residues R_5, R_6, R_7 and R_8 are hydrogen, or of pharmaceutically useful salts of such compounds with at least one salt-forming group for the preparation of pharmaceutical preparations for use as anti-tumor agents in warm-blooded animals, including humans.

5. Use as in one of the claims 1-4, in which in the compound of formula I at least two of the residues R_5, R_6, and R_8 are each hydrogen.

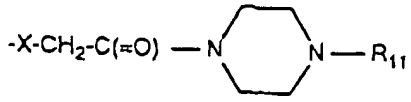
6. Use as in one of the claims 1-4, in which in the compound of formula I R_5, R_6, and R_8 are each hydrogen.

7. Use as in one of the claims 1-4, in which in the compound of formula I R_1, R_2, R_4, R_5, R_6 and R_8 are each hydrogen, R_3 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, –oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-yl-iodide, dimethylamino-phenyl or N-acetyl-N-methyl-aminophenyl, and R_7 is C_1-C_6-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono-(C_1-C_3-alkyl)-amino, di-(C_1-C_3-alkyl)-amino, C_2-C_4-alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di-(C_1-C_3-alkyl)-sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl, or a residue of one of the formulas:

$-CO_2R$, $-NH-C(=O)-R$, $-N(R)-C(=O)-R$, $-O-(CH_2)_n-N(R)-R$, $-C(=O)-NH-(CH_2)_n-N(R)R$, $-CH(CH_3)-NH-CHO$, $-C(CH_3)=N-OH$, $-C(CH_3)=N-O-CH_3$,
$-C(CH_3)-NH_2$, $-NH-CH_2-C(=O)-N(R)R$,



$-(CH_2)_m-R_{10}$, $-X-(CH_2)_m-R_{10}$ or



in which R stends for C_1-C_3-alkyl, X for oxygen or sulfur, m [typo in orlginal] for 1, 2 or 3, n for 2 or 3, R_9 for hydrogen, C_1-C_3-alkyl, C_1-C_3-alkoxy, chlorine, bromine, iodine or trifluoromethyl, R_{10} for 1H-imidazol-1-yl or morpholinyl, and R_{11} for C_1-C_3-alkyl or unsubstituted phenyl or phenyl mono-substituted by C_1-C_3-alkyl,

halogen or trifluoromethyl.

8. Use as in one of the claims 1-4 in which, in the compound of formula I, R_1, R_2, R_4, R_5, R_6 and R_9 are each hydrogen, R_3 is 3-pyridyl and R_7 is 1H-imidazol-1-yl, amino, trifluoromethyl, chlorine, or a residue of formula $-CO_2R$ or $-C(=O)-NH-(CH_2)_n-N(R)-R$, in which R is hydrogen or methyl in each case and n is 3.

9. Use as in one of the claims 1-4, in which N-(3-1H-imidazol-1-yl-phenyl)-4-(3-pyridyl)-2-pyrimidinamine [typo in original] or a pharmaceutically useful salt thereof is used as the compound of formula I.

10. Use as in one of the claims 1-4, in which is used N-(3-trifluoromethyl-phenyl)-4-(3-pyridyl)-2-pyrimidinamine [typo in original] or a pharmaceutically useful salt thereof is used as the compound of formula I.

11. Use as in one of the claims 1-4, in which N-(3-chloro-phenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically useful salt thereof is used as the compound of formula I.

12. Use as in one of the claims 1-4, in which N-(3-amino-phenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically useful salt thereof is used as the compound of formula I.

13. Use as in one of the claims 1-4, in which N-(3-methoxycarbonyl-phenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically useful salt thereof is used as the compound of formula I.

14. Use as in one of the claims 1-4, in which N-(3-[3-amino-propylamino-carbonyl]-phenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically useful salt thereof is used as the compound of formula I.

European Patent Office

Application number EP 93 81 0595

EUROPEAN PARTIAL SEARCH REPORT

which according to Rule 45 of the European Patent Agreement is valid for the further process as European Search Report

PERTINENT DOCUMENTS			
Category	Document reference with information, as required, on the relevant parts	Relates to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D, A	EP-A-0 233 461 (AMERICAN CYANAMID COMP.) August 26, 1987 * Entire document * - - -	1-14	A61K31/505
A	EP-A-0 453 731 (AMERICAN CYANAMID COMP.) October 30, 1991 * Entire document * - - -	1-14	
A	EP-A-0 164 204 (FISONS) December 11, 1985 * Entire document * - - -	1-14	
			TECHNICAL AREAS SEARCHED (Int.Cl.5) A61K

INCOMPLETE SEARCH

In the opinion of the Search Department, the present European patent application complies so little with the provisions of the European Patent Agreement that it is not possible on the basis of a few patent claims to implement meaningful investigations on the state of the art.
Completely searched patent claims:
Incompletely searched patent claims:
Unsearched patent claims:
Reason for the limitation of the research:

See Supplementary sheet C

Site of search	Date of completion of search	Examiner
The HAGUE	December 27, 1993	Krautbauer, B.

CATEGORY OF CITED DOCUMENTS

X:	Particularly relevant if taken alone	P:	Intermediate document
Y:	Particularly relevant if combined with another document of the same category	T:	Theory or principle underlying the invention
A:	Technological background	D:	Document cited in the application
O:	Non-written disclosure	L:	Document cited for other reasons
E:	Earlier patent doc. but published on, or after, the filing date	&	Member of same patent family, Corresponding document

INCOMPLETE SEARCH

Completely searched patent claims: 9-14
Incompletely searched patent claims: 1-8

Basis: Based on the large number of theoretically possible substances that result from the Markush formula used, the search had to be limited to the substances named explicitly in the claims and also to the general inventive concept.